Exhibit I

RESPONSE UNDER 37 CFR 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP 1804

#33

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Katherine Gordon and Suzanne Groet

Serial No: 07/426,464 Examiner: J. Chambers

Filed: October 20, 1989 Art Unit: 1804

For: TRANSGENIC ANIMALS SECRETING DESIRED PROTEINS INTO MILK

DECLARATION UNDER RULE 132

The Honorable Commissioner
of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, KATHERINE GORDON, declare and state as follows:

1. I am an applicant of the above-identified patent application, and a co-inventor of the subject matter described and claimed therein.

2. I hold a Ph.D. Degree in Biology from Wesleyan University, and I have worked in the field of molecular biology and gene expression for approximately 14 years. Currently, I am President of Biodynamics, a firm which supplies professional consulting services to the biotechnology industry. I was previously employed by Integrated Genetics, Inc. of Framingham, Massachusetts

as an Associate Director, and during my tenure at Integrated Genetics I was responsible for the technical aspects of the transgenic program.

3. I have read and I am generally familiar with the outstanding Official Action of April 7, 1992, in the above-identified patent application. The Official Action states that the claims pending in the application are not enabled by the disclosure since, inter alia, there is no indication that, as of the effective filing date, a transgenic mammal had been made that could produce a protein of interest in its milk. The Examiner has also indicated that the claimed invention should be limited to transgenic mice and to a specific promoter, i.e. the WAP promoter.

4. It is my opinion that the state of transgenic technology as of the filing date of the above-identified patent application, as shown by technical publications available at that time, would have been sufficient to enable one skilled in the art to prepare a transgenic mammal which could express a foreign protein. The inventive feature of the present invention, namely the preparation of a transgenic mammal capable of producing a protein of interest in its milk, is readily enabled by the combined teachings of these prior technical publications and the present disclosure. This opinion is supported by the Gordon et al. (Exhibit A) and Hammer et al. (Exhibit B) references.

5. Gordon et al. (no relation to me) describes a detailed procedure for the preparation of transgenic mice with genetic material, including a detailed description of microinjection and reimplantation of the embryos, the particular surgical equipment required, a description of the embryo medium, and an assessment of the mating efficiency. With some minor refinements, this procedure is still in use today, and has been used over the intervening years by several hundred research laboratories as a standard protocol for the preparation of transgenic mice.

6. Of course, it was not possible to predict with absolute certainty at the time of filing the original patent application that each and every injected egg would successfully lead to a transgenic mouse. The Gordon et al. reference specifically states that only 10-20% of microinjected embryos will survive until birth, with 15-30% of those born carrying transferred DNA sequences. These statistics are largely dependent on the skill of the technician, and they are still basically relevant today. This is the case because transgenics is not an exact science and, even with an extremely detailed protocol, the overall success rate of the procedure is difficult to predict. However, it is clear to me that at least <u>some</u> transgenic mammals would have been successfully prepared using the Gordon et al. procedure, and that <u>some</u> of these mice would be expected to produce milk containing the protein of interest.

7. Reference is also made to Exhibit C which I believe further supports my position concerning sufficiency of enablement as stated in paragraphs 5 and 6 above. Exhibit C is a scientific paper which I co-authored. This paper describes the production of biologically active tPA from transgenic mice following the procedure of the present application and techniques which are well known in the art. The paper conclusively demonstrates that the invention described in the above-identified patent application was actually reduced to practice at least as early as June 16, 1987, the date of receipt of the paper. However, the techniques employed in the paper were available to anyone skilled in the art as of the effective filing date of the present application.

8. It is also my opinion that other technical publications available as of the filing date provide ample support for the preparation of transgenic mammals other than mice, such as pigs, cows, rabbits, goats and sheep. The Hammer et al. reference, Exhibit B, is enclosed as one specific example.

9. Once the transgenic mammal has been produced, the expressed protein can be obtained from the milk of the transgenic mammal using isolation and purification techniques which are conventional in the art.

10. The vector used to transform the embryo includes a promoter which can be a milk serum promoter or a casein protein promoter. The milk serum protein promoters are

one class of promoter which includes the WAP (whey acid protein) promoter as one specific member of the class. There are approximately ten (10) types of milk serum protein promoters, and all of these promoters are similar in function and would be expected to be operable in the present invention. The casein promoters are another class of promoter which is operable in the present invention. The operability of the casein promoters is supported by U.S. Patent No. 4,873,316, to Meade et al., enclosed as Exhibit D, which conclusively demonstrates the operability of this promoter.

11. I have also reviewed in detail the references cited in the outstanding Official Action. None of these references describe the use of a secretion signal in the DNA construct. Without this critical component, it would not be possible to secrete the protein of interest in the milk of a transgenic mammal.

Declarant further states that all statements made herein of her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: July 8 1992

KATHERINE GORDON